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NOVEL COMPOUNDS

The present invention provides new triazolo[4,5-*d*]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

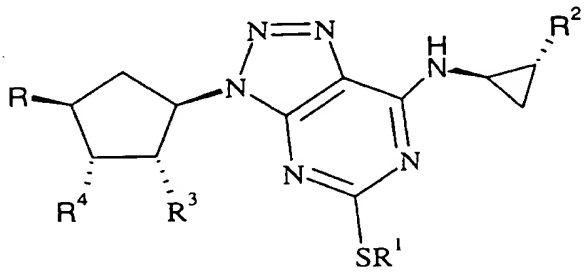
A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross linking of platelets by binding of fibrinogen to a membrane binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K.L. et. al. (1994) *Circulation* **90**, pp.1638-1642).

It has been found that ADP acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT, serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion (see e.g. Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp. 81-106; Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp.159-168). Aspirin has no effect on aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow. ADP-induced platelet aggregation is mediated by the P_{2T}-

receptor subtype uniquely located on the platelet membrane. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents. Accordingly there is a need to find P_{2T}-antagonists as anti-thrombotic agents.

PCT/SE98/01393 discloses a series of triazolo[4,5-*d*]pyrimidine compounds having activity as P_{2T}-antagonists. It has now been found that certain compounds within the scope of PCT/SE98/01393 but not specifically disclosed therein exhibit high potency combined with surprisingly high metabolic stability and bioavailibility, such that the predicted therapeutic dose for prolonged inhibition of aggregation in man shows advantage.

In a first aspect the invention therefore provides a compound of formula (I):



(I)

wherein:

R^1 is a C_{3-5} alkyl optionally substituted by one or more halogen atoms;

R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;

R^3 and R^4 are both hydroxy;

R is a group XOH where X is CH_2 or OCH_2CH_2 or a bond

or a pharmaceutically acceptable salt or solvate thereof,

provided that:

when X is CH_2 or a bond R^1 is not propyl.

when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine.

when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

Alkyl groups, whether alone or as part of another group are straight chained and fully saturated.

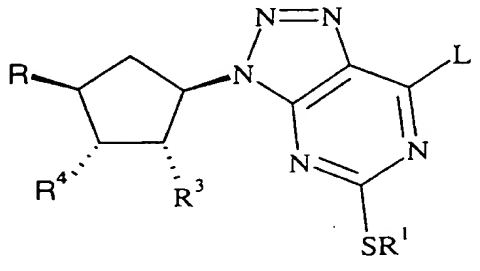
Suitably R^1 is a C_{3-5} alkyl optionally substituted by one or more fluorine atoms. Preferably R^1 is C_{2-4} alkyl substituted by trifluoromethyl. More preferably R^1 is 3,3,3,-trifluoropropyl.

Suitably R^2 is phenyl. Preferably the phenyl group is optionally substituted by one or more fluorine atoms, more preferably R^2 is 4-fluorophenyl or 3,4-difluorophenyl.

Suitably R is a group XOH where X is CH_2 or OCH_2CH_2 or a bond
Preferably R is a group CH_2OH or OCH_2CH_2OH.

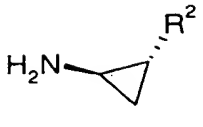
Particularly preferred compounds include:
[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol,
[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol ,
[1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-(2-(3,4-Difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol,
[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol
and pharmaceutically acceptable salts and solvates thereof.

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises:
(a) reacting a compound of formula (II):



(II)

where R, R^1, R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R^3 and R^4 together form a bond, and L is a leaving group with a compound of formula (III):

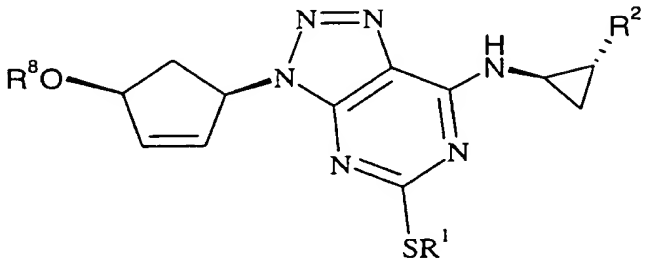


(III)

where R^2 is as defined in formula (I) or is a protected derivative thereof,

or where X is a bond:

(b) hydroxylation of a compound of formula (IV):



(IV)

where R^1, R^2 are as defined in formula (I) and R^8 is H or $CH_2CH_2OP_3$ where P_3 is H or a protecting group or R^8 is CH_2COOR' where R' is C_{1-6} alkyl or benzyl,
and optionally thereafter (a) or (b) and in any order:
converting one or more functional groups into a further functional groups
removing any protecting groups
forming a pharmaceutically acceptable salt or solvate.

Compounds of formula (II) can be reacted with amines of formula (III) in the presence of a base such as a tertiary organic amine in an inert solvent such as dichloromethane at ambient or elevated temperature. Other suitable bases include inorganic bases such as potassium carbonate.

The hydroxy groups R^3 and R^4 can be protected as groups OP^1 and OP^2 where P^1 and P^2 are protecting groups. Examples of suitable protecting groups in compounds of formula (II) are C_{1-6} alkyl (preferably methyl), benzyl,
$(C_{1-6}alkyl)_3Si$ (preferably t-butyldimethylsilyl), and a $C(O)C_{1-6}$alkyl group such as acetyl.
Preferably the two groups P^1 and P^2 together with the atoms to which they are attached form an alkylidene ring such as a methylidene or isopropylidene ring. Alternatively P^1 and P^2 can form an alkoxymethylidene ring such as ethoxymethylidene.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

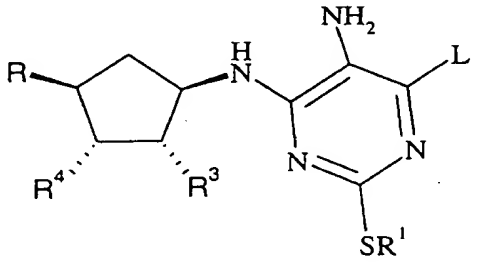
Ester protecting groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to 100°C, preferably the temperature is around room temperature; or by acidic hydrolysis using a mineral acid such as HCl or a strong organic acid such as trichloroacetic acid in a solvent such as aqueous 1,4-dioxane.

Trialkylsilyl protecting groups can be removed by the use of, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or hydrogen fluoride.

When one or both of P^1 and P^2 are C_{1-6} alkyl, deprotection can be achieved using boron tribromide.

Benzyl groups can be removed by hydrogenolysis using a transition metal catalyst, for example palladium on charcoal, under an atmosphere of hydrogen, at a pressure of from 1 to 5 bar, in a solvent, such as acetic acid.

A compound of formula (II) can be prepared by diazotising a compound of formula (V):

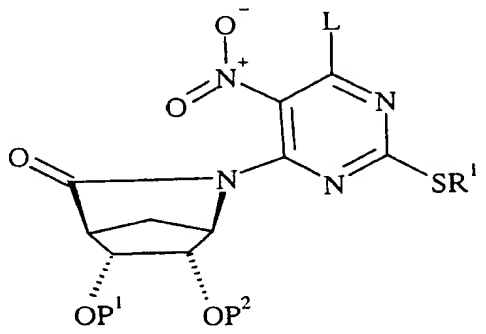


(V)

wherein R^1 is as defined in formula (I) and R is as defined in formula (I) or a protected derivatives thereof or is OCH_2CO_2R' wher R' is C_{1-6} alkyl or benzyl, and L is as defined above and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R^3 and R^4 together form a bond, with a metal nitrite, for example an alkali metal nitrite, especially

sodium nitrite in dilute aqueous acid, for example 2M HCl, or with a C_{1-6}-alkyl nitrite in an inert solvent, at a temperature of from -20 to 100°C; preferred conditions are isoamyl nitrite in acetonitrile at 80°C.

A compound of formula (V) wherein R is CH_2OH, R^3 and R^4 are hydroxyl or protected derivatives thereof and L is as defined above, can be prepared by reducing a compound of formula (VI):

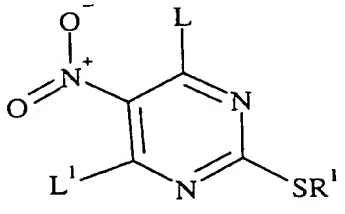


(VI)

wherein R^1, L, P^1 and P^2 are as defined above. The reduction of the nitro group can be carried out for example by using hydrogenation with a transition metal catalyst at a temperature around room temperature, for example palladium on charcoal under an atmosphere of hydrogen, preferably at a pressure from 1 to 5 atmospheres, in a solvent, for example ethanol, or by using iron in an acidic solvent such as acetic acid at a temperature of about 100°C.

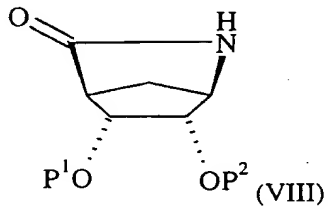
Reduction of the lactam can be carried out using complex metal hydrides such as lithium aluminium hydride in a solvent such as ether or preferably by using sodium borohydride in a suitable solvent such as methanol.

A compound of formula (VI) can be prepared by reacting a compound of formula (VII):



(VII)

wherein L and R^1 are as defined above and L^1 is a leaving group, for example a halogen atom, wherein L and L^1 are preferably the same, with a compound of formula (VIII):

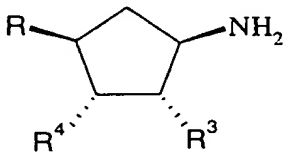


(VIII)

wherein P^1 and P^2 are as defined above, in the presence of a base such as C_{1-6}-alkyl-M or MH wherein M is a metal ion, for example n-butyl lithium, in an inert solvent, such as tetrahydrofuran (THF), at a temperature of from -10 to 100°C. Preferably sodium hydride is used in THF at room temperature.

One or more functional groups can be converted into further functional groups using standard chemistry. A compound where X is a bond can be converted to a compound where X is $O(CH_2)_2$ by treatment with base followed by LY where L is a leaving group and Y is $(CH_2)_2OH$ or a protected version thereof or Y is CH_2COOR' where R' is C_{1-6} alkyl or benzyl. A compound where Y is CH_2COOR' may be converted into a compound where Y is $(CH_2)_2OH$ by reduction, for example using DIBAL-H®. The group SR^1 can be interconverted by oxidation of the sulfur, for example using oxone™ or mCBPA, followed by treatment with a compound $R^{1'}$-SM where $R^{1'}$ is a different R^1 group and M is a metal such as sodium. Alternatively the product of the sulfur oxidation may be treated with MSH where M is a metal such as sodium, followed by treatment with a base and $R^{1'}X$ where $R^{1'}$ is a different R^1 group and X is a leaving group. Suitable bases include *N,N*-diisopropylethylamine.

Compounds of formula (V) can also be prepared by treating a compound of formula (XI)

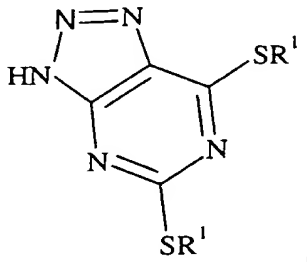


(XI)

where R , R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R^3 and R^4 together form a bond, with a compound of formula (VII) as defined above, followed by reduction of the nitro group. The reaction is carried out in an inert solvent such as

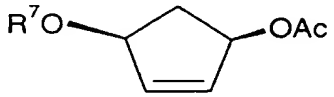
dichloromethane or 1,4-dioxane in the presence of a non-nucleophilic base such as *N,N*-diisopropylamine at a temperature of about -20°C to about 150°C, preferably at ambient temperature.

Compounds of formula (V) where R^3 and R^4 form a bond and L is SR^1 can be prepared by reacting a compound of formula (XII):



(XII)

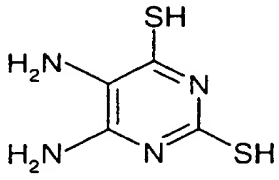
in which R^1 groups are as defined in formula (I) or are C_{3-6}-alkyl with a compound of formula (XIII):



(XIII)

in which R^7 is H or a protected derivative thereof. The reaction can be carried out in the presence of a suitable transition metal complex, preferably tetrakistriphenylphosphine palladium (0).

Compounds of formula (XII) can be prepared from compounds of formula (XIV):



(XIV)

by reacting with a compound R^1X where R^1 is as defined in formula (I) and X is a leaving group such as halo, followed by cyclisation.

Compounds of formula (XI) where R is OH or a protected version thereof and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof may be prepared from compounds of formula (XIII) by treatment with a bisester of imidodicarbamic acid using palladium catalysis followed by hydroxylation of the double bond. Preferably imidodicarbonic acid, bis-(1,1-dimethylethyl)ester and tetrakistriphenylphosphine palladium (0) are used followed by osmium tetroxide.

The amines of formula (III) can be prepared using procedures described in H Nishiyama *etal*, Bull. Chem. Soc., Jpn., 1995, **68**, 1247, P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1, Amines and Related Compounds; Optical Resolution and Information Centre: Manhattan College, Riverdale, NY, 1978, p120, J. Vallgarda *etal*, J. Chem. Soc. Perkin 1, 1994, 461. Certain amines of formula (III) are novel compounds and form a further aspect of the invention.

All novel intermediates form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C_{1-6}-alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, THF or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary revascularisation procedures including angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and

other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

According to the invention there is further provided the use of a compound according to the invention in the manufacture of a medicament for the treatment of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and angina, especially unstable angina. The invention also provides a method of treatment of the above disorders which comprises administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to the invention.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the

tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol , mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The invention is illustrated by the following examples. In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak®, Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2)) was carried out using Fisher Matrix silica, 35-70 μm. For examples which showed the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

[1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

a) [3a*S*-[1(*E*),3aα,6α,7aβ]]-1-[3-(4-Fluorophenyl)-1-oxo-2-propenyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

A mixture of 3-(4-fluorophenyl)-2-propenoic acid (3.0g) and thionyl chloride (5.0ml) was stirred at 70°C for 1 hour, the reaction mixture was then concentrated under reduced pressure. The residue was azeotroped twice with dichloromethane then dissolved in toluene (10ml). To a suspension of sodium hydride (60% dispersion in oil; 0.99g) in toluene (40ml) was added a solution of [3a*S*-(3aα,6α,7aβ)]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide (3.89g) in toluene (40ml) and the mixture stirred for 30 minutes. To the reaction mixture was then added the solution described above and the resulting suspension was stirred for 16 hours. Water (200ml) was added, the organics collected and the aqueous extracted into dichloromethane (3x100ml). The organics were combined, dried and concentrated. Recrystallisation (ethanol) gave the subtitle compound as colourless needles (5.92g).

MS (APCI) 364 ($M+H^+$,100%)

b) [3a*S*-[1(1*S,2*S**),3aα,6α,7aβ]]-1-[[2-(4-Fluorophenyl)cyclopropyl]carbonyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide**

A solution of diazomethane (2.9g) in ether (150ml) (prepared as described in Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, Longman Scientific and Technical, p432) was added to a solution of the product of step a) (5.90g) and palladium(II) acetate (18mg) in dichloromethane (350ml) at 0°C and the reaction mixture stirred at 0°C for 5 hours. Acetic acid (5ml) was added and the reaction mixture was then washed with saturated sodium bicarbonate solution (200ml) and the organics filtered through a plug of silica. After concentrating *in vacuo*, the residue was recrystallised (ethanol) to give the subtitle compound as colourless needles (3.81g).

MS (APCI) 378 ($M+H^+$,100%)

product of step d) (0.75g) in dichloromethane (25ml). The reaction mixture was stirred at room temperature for 3 hours, then washed with water, dried and evaporated. The residue was purified (SiO_2, ethyl acetate:isohexane 1:1 as eluent) to afford the subtitle compound (1.25g).

MS (APCI) 515 ($M+H^+$, 100%)

f) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

3-Chloroperoxybenzoic acid (70%, 1.8g) was added to a suspension of the product of step e) (1.25g) in ethanol (25ml) and the resulting solution stirred at room temperature for 2 hours. The reaction mixture was concentrated and the residue taken up in ethyl acetate (500ml), washed with 10% aqueous sodium metabisulfite solution (2 x 100ml) and 10% aqueous sodium bicarbonate solution (2x100ml) then dried and concentrated to afford the subtitle compound (1.4g).

MS (APCI) 547 ($M+H^+$, 100%)

g) [[3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropy)lthio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

Sodium hydrosulfide hydrate (1.4g) was added to a solution of the product of step f) (1.4g) in dimethyl sulphoxide (20ml) and the solution stirred at room temperature for 1.5 hours. Brine (150ml) was added and the mixture acidified with acetic acid then extracted with ethyl acetate (3x100ml). The organic phase was dried and concentrated and the residue azeotroped with toluene (3x100ml). The residue was dissolved in *N,N*-dimethylformamide (20ml) then *N,N*-diisopropylethylamine (0.33g) and 3,3,3-trifluoropropylbromide (0.48g) added. After stirring at 50°C for 30 minutes the reaction mixture was diluted with ethyl acetate (100ml) then washed with aqueous brine (3x100ml), dried and concentrated then the residue purified (SiO_2, isohexane:ethyl acetate 1:1 as eluant) to afford the subtitle compound (1.4g).

MS (APCI) 569 ($M+H^+$, 100%)

c) (1*R-trans*)-2-(4-Fluorophenyl)-cyclopropanecarboxylic acid

A suspension of the product from step b) (3.74g) and lithium hydroxide monohydrate (4.11g) in tetrahydrofuran (100ml)/ water (3ml) was stirred at 50°C for 24 hours. The reaction mixture was concentrated *in vacuo*, and the residue dissolved in water (100ml), acidified with 2N HCl and extracted into dichloromethane (3x75ml).
The organics were dried and concentrated. Purification (SiO_2, isohexane:diethylether 2:1 as eluant) gave the subtitle compound as a colourless solid (1.78g).

MS (APCI) 179 ($M\text{-}H^+$,100%)

d) (1*R-trans*)-2-(4-Fluorophenyl)cyclopropanamine, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1)**

To a solution of the product from step c) (1.78g) and triethylamine (2.7ml) in acetone /water (10:1, 23ml) at 0 °C was added ethyl chloroformate (2.0ml) over 5 min. The solution was maintained at 0 °C for 30 minutes before addition of sodium azide (1.52g) in water (6ml). After a further hour, water (350ml) was added and the reaction mixture extracted with toluene (3x100ml). The organic extracts were combined and dried, then heated at reflux for 2 hours behind a blast screen. After cooling the solution, 6N HCl (50ml) was added and the mixture heated at reflux for 3 hours. Water (150ml) was added and the aqueous phase basified with 2N NaOH (aq), then extracted into dichloromethane (3x100ml). The organic phase was dried and concentrated. The amine was dissolved in ethanol (5ml) and a solution of L-tartaric acid (1.48g) in ethanol (20ml) was added. After 20 minutes the solid was collected affording the subtitle compound as colourless needles (1.12g).

NMR δH (d_6-DMSO) 1.07-1.39 (1H, m), 1.22-1.29 (1H, m), 2.16-2.23 (1H, m), 2.64-2.70 (1H,m), 3.95 (2H, s), 7.06-7.19 (4H, m)

e) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

N,*N*-Diisopropylethylamine (1.29g) was added to a solution of [3a*R*-(3aα,4α,6α,6aα)]-6-[7-chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in WO 9703084) (1.0g) and the

h) [1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

A solution of the product from step g) (1.4g) in trifluoroacetic acid (10ml) and water (2ml) was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate (400ml) then washed with sodium bicarbonate solution (400ml), dried and evaporated. The residue was purified (SiO_2, methanol:chloroform 3:47 as eluant) to afford the title compound (0.44g).

MS (APCI) 529 ($M+H^+$,100%)

NMR δH (d_6-DMSO) 9.42 (1H, d), 7.27-7.22 (2H, m), 7.14-7.08 (2H, m), 5.01-4.95 (2H, m), 4.73-4.70 (2H, m), 4.44-4.41 (1H, m), 3.87-3.84 (1H, m), 3.50-3.45 (2H, m), 3.26-3.13 (3H, m), 2.60-2.55 (1H, m), 2.28-2.20 (2H, m), 2.10-2.06 (1H, m), 1.90-1.80 (1H, m), 1.49-1.46 (1H, m), 1.33-1.30 (1H, m).

Example 2

[1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

a) [3a*S*-[1(*E*),3aα,6α,7aβ]]-1-[3-(3,4-Difluorophenyl)-1-oxo-2-propenyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

The subtitle compound was prepared according to the method of Example 1, step a) using 3-(3,4-difluorophenyl)-2-propenoic acid.

MS (APCI) 382 ($M+H^+$, 100%)

b) [3a*S*-[1(1*S,2*S**),3aα,6α,7aβ]]-1-[[2-(3,4-Difluorophenyl)cyclopropyl]carbonyl]-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide**

The subtitle compound was prepared according to the method of Example 1, step b) using the product of step a).

MS (APCI) 396 ($M+H^+$, 100%)

c)(1*R-trans*)-2-(3,4-Difluorophenyl)-cyclopropane carboxylic acid

The subtitle compound was prepared according to the method of Example 1, step c) using the product of step b).

NMR δH ($CDCl_3$) 7.06 (1H, dt, *J*=10.0, *J*=8.5 Hz), 6.93-6.80 (2H, m), 2.58-2.52 (1H, m), 1.88-1.82 (1H, m), 1.66 (1H,dt, *J*=9.2, *J*=5.2 Hz), 1.34 (1H, ddd, *J*=8.5, *J*=6.5, *J*=4.8 Hz).

d)(1*R-trans*)-2-(3,4-Difluorophenyl)cyclopropanamine, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1)**

The subtitle compound was prepared according to the method of Example 1, step d) using the product of step c).

MS (APCI) 170 ($M+H^+$, 100%)

e)[3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]-6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol**

Isoamyl nitrite (5.1ml) was added to a solution of [3a*R*-(3aα,4α,6α,6aα)]-6-[[5-amino-6-Chloro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]-amino]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in WO 9703084) (8.1g) in acetonitrile (1000ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated and purified (SiO_2, dichloromethane:ethyl acetate 4:1 as eluant) to afford an intermediate which was converted to the subtitle compound by the method of example 1, step e) using the product of step d).

MS (APCI) 587 ($M+H^+$, 100%)

f) [1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

Prepared according to the method of example 1, step h) using the product of step e).

MS (APCI) 547 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.43 (1H, d), 7.35-7.28 (2H, m), 7.14-7.02 (1H, m), 5.01-4.96 (2H, m), 4.72-4.69 (2H, m), 4.42 (1H, q), 3.87-3.84 (1H, m), 3.50-3.44 (2H, m), 3.25-3.12 (3H, m), 2.58-2.50 (2H, m), 2.28-2.21 (3H, m), 1.85-1.80 (1H, m), 1.52-1.50 (1H, m), 1.39-1.37 (1H, m).

Example 3

[1S-(1a,2a,3b(1S*,2R*),5b)]-3-[7-(2-(3,4-Difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol,

a) (1*R-cis*)-Bis(1,1-dimethylethyl)-4-hydroxy-2-cyclopentenylimidodicarbonate

To a suspension of ether washed sodium hydride (60% dispersion in oil; 0.31g) in THF (30ml) was added imidodicarbonic acid bis-(1,1-dimethylethyl)ester (1.84g). The mixture was stirred at 40°C for 1 hour. To the mixture, at ambient temperature, was then added (1*S-cis*)-4-acetoxy-2-cyclopenten-1-ol (0.5g) and tetrakis(triphenylphosphine)palladium (0) (0.18g). The reaction mixture was stirred for 24 hours then purified (SiO_2, ethyl acetate: hexane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.90g).

NMR δH (d_6-DMSO) 1.43 (18H, s), 1.61 (1H, ddd, *J*=12.3, 7.7, 6.4 Hz), 2.54 (1H, dt, *J*=12.6, 7.4 Hz), 4.51-4.57 (1H, m), 4.86 (1H, tq, *J*=8.0, 1.8 Hz), 4.91 (1H, d, *J*=5.4 Hz), 5.71-5.77 (2H, m).

b) [1*R*-(1α,2β,3β,4α)]-2,3,4-Trihydroxy-cyclopentenylimidodicarbonic acid, bis(1,1-dimethylethyl) ester

To a solution of the product of step a) (17.1g) in THF (500ml)/water (50ml) was added *N*-methylmorpholine-*N*-oxide (9.4g) followed by osmium tetroxide (10ml, 2.5% solution in *t*-butanol). The mixture was stirred at room temperature for 4 days then treated with sodium hydrosulphite (6.0g). The suspension was filtered through celite and the product purified (SiO_2, ethyl acetate: hexane 1:1 as eluant) to afford the subtitle compound (19.1g).

NMR δH (d_6-DMSO) 1.44 (18H, s), 1.46-1.60 (1H, m), 1.97-2.05 (1H, m), 3.55-3.58 (1H, m), 3.66-3.73 (1H, m), 4.11-4.21 (2H, m), 4.54 (1H, d, *J*=4.8 Hz), 4.56 (1H, d, *J*=5.9 Hz), 4.82 (1H, d, *J*=4.6 Hz)

c) [3a*R*-(3aα,4α,6α,6aα)]-6-Amino-tetrahydro-2,2-dimethyl- 4*H*-cyclopenta-1,3-dioxol-4-ol, hydrochloride

The product from step b) (17.4g) in 6M HCl (100ml)/methanol (500ml) was stirred for 18 hours. The mixture was evaporated and then azeotroped with toluene (4 x 200ml) to give a colourless powder (8.7g). This solid was suspended in acetone (250ml) containing 2,2-dimethoxypropane (25ml) and cHCl (0.2ml) then heated under reflux for 2 hours. The mixture was cooled, evaporated and azeotroped with toluene (3 x 200ml). The residue was dissolved in 20% aqueous acetic acid and stirred for 2 hours. The mixture was evaporated and azeotroped with toluene (4 x 200ml) to afford the subtitle compound (10.1g).

MS (APCI) 174 ($M+H^+$, 100%)

d) [3a*R*-(3aα,4α,6α,6aα)]-6-[[6-Chloro-5-nitro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

A solution of the product from step c) (10.0g) and *N,N*-diisopropylethylamine (35ml) in THF (600ml) was stirred for 1 hour. The mixture was filtered and the solution was added over 1 hour to a solution of 4,6-dichloro-5-nitro-2-(propylthio)-pyrimidine (prepared as described in WO 9703084) (25.6g) in THF (1000ml) and stirred for a further 2 hours. The solvent volume was reduced *in vacuo* and ethyl acetate was added (1000ml). The mixture was washed with water and the organic layers were dried, evaporated and purified (SiO_2, isohexane-ethyl acetate as eluant) to afford the subtitle compound (14.2g).

MS (APCI) 405 ($M+H^+$, 100%)

e) [3a*R*-(3aα,4α,6α,6aα)]-6-[[5-Amino-6-chloro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

Iron powder (3.0g) was added to a stirred solution of the product of step d) (2.7g) in acetic acid (100ml). The reaction mixture was stirred at room temperature for 2 hours, concentrated to

half volume, diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to afford the subtitle compound (2.0g).

MS (APCI) 375 ($M+H^+$, 100%)

f) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

Isoamyl nitrite (1.1ml) was added to a solution of the product of step e) (2.0g) in acetonitrile (100ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated and purified (SiO_2, ethyl acetate:isohexane 1:3 as eluant) to afford the subtitle compound (1.9g).

MS (APCI) 386 ($M+H^+$, 100%)

g) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol

The product of step f) (13.2g) in THF (200ml) containing 0.88 ammonia (5ml) was stirred for 2 hours then concentrated to dryness and the residue partitioned between water and ethyl acetate. The organics were dried and then concentrated to afford the subtitle compound (12.5g).

MS (APCI) 367 ($M+H^+$, 100%).

h) [3a*R*-(3aα,4α,6α,6aα)]-[[6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester

To a solution of the product of step g) (0.50g) in THF (25ml) at 0°C, was added butyllithium (0.62ml of 2.5N in hexanes). After 20 minutes, the suspension was treated with a solution of trifluoromethanesulfonyloxy-acetic acid methyl ester (0.34g) (prepared according to the method of Biton, Tetrahedron, 1995, **51**, 10513) in THF (10ml). The resulting solution was allowed to warm to room temperature then concentrated and purified (SiO_2, ethyl acetate: hexane 4:6 as eluant) to afford the subtitle compound (0.25g).

MS (APCI) 439 ($M+H^+$, 100%).

i) [3a*R*-(3aα,4α,6α,6aα)]-[[6-[7-Bromo-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester

The product from step h) (1.1g) and isoamylnitrite (2.4ml) in bromoform (30ml) was heated at 80°C for 30 minutes . The cooled reaction mixture was purified (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the subtitle compound (0.44g).

MS (APCI) 502/4 ($M+H^+$), 504 (100%).

j) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-[[6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-*4H*-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, methyl ester**

To a mixture of the products from step i) (0.80g) and Example 2, step d) (0.61g) in dichloromethane (25ml) was added *N,N*-diisopropylethylamine (0.85ml). The resulting solution was then stirred at room temperature for 16 hours then concentrated *in vacuo*. Purification (SiO_2; isohexane:ethylacetate 3:1 as eluant) gave the subtitle compound as a colourless foam (0.77g).

MS (APCI) 591 ($M+H^+$, 100%).

k) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[[7-[2-(3,4-Difluorophenyl) cyclopropyl]amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol**

DIBAL-H® (1.0M solution in hexanes, 5.15ml) was added to an ice-cooled solution of the product of step j) (0.76g) in tetrahydrofuran (1ml) and the solution stirred at this temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (75ml). A saturated aqueous solution of sodium potassium tartrate (75ml) was added and the mixture stirred vigorously for 16 hours. The organics were collected and the aqueous re-extracted with ethyl acetate (2x50 ml). The combined organics were dried and concentrated and the residue purified (SiO_2, isohexane:ethylacetate 1:1 as eluant) to give the subtitle compound (0.63g).

MS (APCI) 563 ($M+H^+$,100%)

l) [1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-(2-(3,4-Difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol

Prepared according to the method of example 1, step h) using the product of step k).

MS (APCI) 523 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 8.95 (1H, d, *J*=3.3 Hz), 7.39-7.21 (2H, m), 7.10-7.00 (1H, m), 5.12 (1H, d, *J*=6.4 Hz), 5.05 (1H, d, *J*=3.6 Hz), 4.96 (1H, q, *J*=9.0 Hz), 4.62-4.54 (2H, m), 3.95 (1H, br s), 3.79-3.73 (1H, m), 3.55-3.47 (4H, m), 3.20-3.13 (1H, m), 2.98-2.81 (2H, m), 2.63 (1H, dt, *J*=13.6, 8.5 Hz), 2.29-2.21 and 2.16-2.09 (1H, m), 2.07-2.00 (1H, m), 1.73-1.33 (4H, m), 0.99 (3H, t, *J*=7.4 Hz).

Example 4

[1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

a) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol

Prepared according to the method of Example 3, step g) using [3a*R*-(3aα,4α,6α,6aα)]-6-[7-chloro-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol (prepared as described in WO 9703084). The crude product was purified (SiO_2, methanol:dichloromethane 1:19 as eluant) to give the subtitle compound.

MS (APCI) 381 ($M+H^+$, 100%).

b) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylsulfonyl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol

Prepared according to the method of example 1, step f) using the product of step a).

MS (APCI) 413 ($M+H^+$, 100%).

c) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol

1-Butanethiol (2.38ml) in DMF (25ml) was added to a suspension of sodium hydride (60%, 1.09g) in DMF (50ml). After 1 hour a solution of the product of step b) (3.66g) in DMF (65ml) was added dropwise and the resulting mixture was stirred overnight. The reaction mixture was added slowly to saturated aqueous sodium bicarbonate (1000ml) and then extracted into ethyl acetate (3 x 200ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified (SiO_2, methanol:dichloromethane 1:19 as eluant) to give the subtitle compound (3.32g).

MS (APCI) 395 ($M+H^+$, 100%).

d) [3a*R*-(3aα,4α,6α,6aα)]-Acetic acid, [[6-[7-amino-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-yl]methyl]ester

To a solution of the product from step c) (3.3g) in dichloromethane (50ml), was added pyridine (2.7ml), 4-dimethylaminopyridine (0.4g) and acetic anhydride (2.0 ml). The mixture was stirred at room temperature overnight, concentrated *in-vacuo* and purified (SiO_2, diethyl ether:isohexane 3:2 as eluent) to give the subtitle compound (2.7g).

MS (APCI) 437 ($M+H^+$, 100%).

e) [3a*R*-(3aα,4α,6α,6aα)]-6-[7-Bromo-5-(butylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate

Prepared according to the method of example 3, step i) using the product of step d).

MS (APCI) 500/502 ($M+H^+$), 500 (100%).

f) [3a*R*-[3aα,4α,6α(1*R,2*S**),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-methanol, acetate**

Prepared according to the method of example 3, step j) using the product of example 2, step d) and the product of step e).

MS (APCI) 589 ($M+H^+$, 100%).

g) [1*R*-[1α,2α,3β(1*R,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol**

The product of step f) (0.64g) in 80% aqueous acetic acid (30ml) was heated at 80°C for 1 hour. The cooled mixture was poured into saturated sodium bicarbonate solution and extracted into ethyl acetate. The organic phase was dried and concentrated *in vacuo* to give a gum which was dissolved in methanol (50ml)/10% aqueous potassium carbonate solution (3ml). The solution was stirred for 30 minutes, neutralised with acetic acid, and concentrated *in vacuo*. Purification (SiO_2, methanol:dichloromethane 1:19 as eluent) gave a solid which was recrystallised (acetonitrile) to give the title compound (0.25g).

MS (APCI) 507 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.34 (1H, br), 7.40-7.23 (2H, m), 7.11-7.00 (1H, m), 5.06-4.93 (2H, m), 4.76-4.67 (2H, m), 4.48-4.38 (1H, m), 3.91-3.84 (1H, m), 3.56-3.39 (2H, m), 3.21-3.08 (1H, m), 3.03-2.83 (2H, m), 2.32-2.17 (1H, m), 2.17-2.03 (2H, m), 1.91-1.77 (1H, m), 1.71-1.32 (4H, m), 1.32-1.17 (2H, m), 0.81 (3H, t).

Pharmacological data

The preparation for the assay of the P_{2T}-receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640G. The

supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137mM, $NaHCO_3$ 11.9mM, NaH_2PO_4 0.4mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37°C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3°C with air excluded. To allow recovery from PGI_2-inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 µl of 50 mM solution with a final concentration of 1mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 µl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 µl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 µl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows.

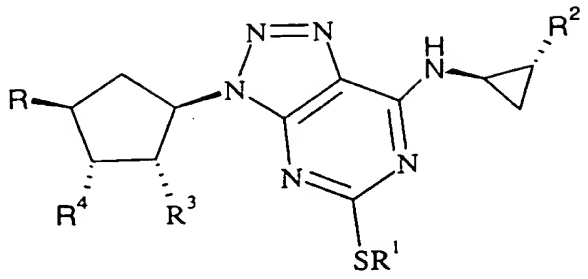
Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX were used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate solution of test compound was added to each well in a volume of 10 µl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 µl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

Claims

1. A compound of formula (I)



(I)

wherein:
R^1 is a C_{3-5} alkyl optionally substituted by one or more halogen atoms;
R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;
R^3 and R^4 are both hydroxy;
R is a group XOH where X is CH_2 or OCH_2CH_2 or a bond
or a pharmaceutically acceptable salt or solvate thereof,
provided that:
when X is CH_2 or a bond R^1 is not propyl.
when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine.
when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

2. A compound according to claim 1 or 2 in which R^1 is C_{2-4} alkyl substituted by trifluoromethyl.

3. A compound according to any one of claims 1 to 3 in which R^2 is a 4-fluorophenyl or 3,4-difluorophenyl group.

4. A compound according to any one of claims 1 to 5 in which R is a group CH_2OH or OCH_2CH_2OH.

5. A compound according to claims 1 which is:
[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol,

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol ,

[1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-(2-(3,4-Difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol,

[1*R*-[1α,2α,3β(1*R**,2*S**),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol

or pharmaceutically acceptable salts or solvates thereof.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

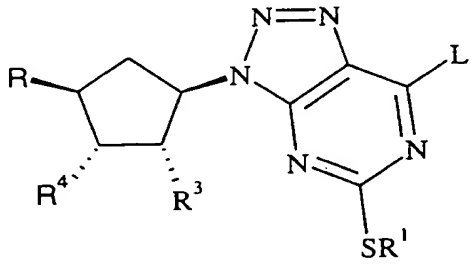
7. A compound according to any one of claims 1 to 6 for use in therapy.

8. A compound according to any one of claims 1 to 6 for use in the treatment or prevention of myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and angina.

9. A compound according to any one of claims 1 to 6 for use in the treatment or prevention of angina.

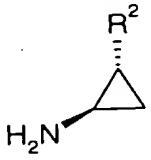
10. A method of treatment a platelet aggregation disorder which comprises administering to a patient suffering from such a disorder a therapeutically effective amount of a according to any one of claims 1 to 6.

11. A process for the preparation of a compound of formula (I) which comprises;
(a) reacting a compound of formula (II):



(II)

where R, R^1, R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, and L is a leaving group with a compound of formula (III), wherein R^2 is as defined in formula (I):



(III)

Where R^2 is as defined in formula (I) or is a protected derivative thereof.

ABSTRACT

The invention provides new triazolo[4,5-*d*]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.